

REMARKS

Claim 24 is amended. Claims 1-36 are currently pending in this application. Claims 1-18 and 25-36 are withdrawn from consideration.

Claim 24 has been amended to replace the word "the" in the phrase "with a nucleic the molecule" with the word "acid" to read "with a nucleic acid molecule".

The specification has been amended to remove the embedded hyperlink.

No new matter is added.

SPECIFICATION

Examiner objected to the specification for containing embedded hyperlinks. Paragraph 97 has been amended to remove the embedded link.

In view of the above comments and foregoing amendments, Examiner is respectfully requested to withdraw the objections to the specification.

CLAIM OBJECTIONS

The Examiner objected to claim 24 for reciting "with a nucleic the molecule". Claim 24 has been amended to replace the word "the" in the phrase "with a nucleic the molecule" with the word "acid" to read "with a nucleic acid molecule", to correct the obvious typographical error.

In view of the above comments and foregoing amendments, Examiner is respectfully requested to withdraw the objections to the claims.

DOUBLE PATENTING

Claim 21 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 21 of copending Application No. 10995951.

Claim 21 of co-pending Application No. 10995951 is being cancelled without prejudice or disclaimer, and no further amendment is required within the present application. Withdrawal of the rejection of claim 21 under 35 U.S.C. 101 is respectfully requested.

Claims 19-20 and 22-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 21 of copending Application No. 10995951.

Claim 21 of copending Application No. 10995951 is being cancelled without prejudice or disclaimer and no further amendment is required within the present application. Withdrawal of the rejection of claim 19-20 and 22-23 is respectfully requested.

CLAIM REJECTIONS - 35 USC § 112

Claims 19-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, Examiner states that the claims are broadly drawn to a method for selectively controlling the transcription of a gene of interest comprising the transformation of a plant with a genetic construct wherein the construct may comprise a multitude of nucleic acid sequences which comprise a ROS operator, and a second transformation of a genetic construct comprising a multitude of ROS repressors. The Examiner states that the specification only provides guidance for the full length sequence of SEQ ID NO: 2 as a functioning ROS repressor.

Applicant respectfully disagrees.

As indicated in Example 2, ROS repressor constructs that express either “wild type ROS” (SEQ ID NO: 1; Figure 1A) or “synthetic ROS” (SEQ ID NO: 2; Figure 1B) were prepared and used to transform plants to obtain the ROS parent. Transgenic lines containing GUS reporter constructs (GUS parent) crossed with transgenic lines containing ROS repressor constructs (ROS parent) exhibit reduced expression of GUS. Results of the cross

are presented in FIG. 9 and demonstrate ROS repression of a gene of interest. The results in FIG. 9A demonstrate that GUS activity is detected in the GUS parent but not in the ROS parent (which does not comprise the GUS construct), or in the progeny of the cross between the ROS and GUS parent. The parent plants each expressed either GUS or ROS RNA as expected (FIG. 9B), yet no GUS RNA was detected in the progeny arising from a cross between the ROS and GUS parents. Southern analysis of the progeny of the cross between the GUS and ROS parents indicates that the progeny plant from the cross between the ROS and GUS parent comprised genes encoding both GUS and ROS (FIG. 9C).

The specification therefore clearly exemplifies the utility of both wild type and synthetic ROS to reduce the expression of a gene of interest in a plant.

Furthermore, the specification discloses a number of different ROS repressors (see para. 65) including:

...microbial ROS repressors, for example but not limited to ROSAR (*Agrobacterium radiobacter*, Brightwell et al. (1995) *Mol. Plant Microbe Interact.* 8: 747-754), MucR (*Rhizobium meliloti*; Keller M et al., (1995) *Mol. Plant Microbe Interact.* 8: 267-277), and ROSR (*Rhizobium elti*; Bittinger et al., (1997) *Mol. Plant Microbe Interact.* 10: 180-186; also see Cooley et al. 1991, *J. Bacteriol.* 173: 2608-2616; Chou et al., 1998, *Proc. Natl. Acad. Sci.*, 95: 5293; Archdeacon J et al. 2000, *FEMS Microbiol Let.* 187: 175-178; D'Souza-Ault M. R., 1993, *J Bacteriol* 175: 3486-3490.

Sequences of these ROS repressors are also provided in FIGS. 1(A) to (C) and (SEQ ID NO's: 1-3 and 21).

Application respectfully submits that a person skilled in the art to which the specification pertains, or with which it is most nearly connected, would be readily able to make and use the invention based on the teachings provided in the disclosure and Applicant should be entitled to fair protection for their invention.

In view of the above comments, Examiner is respectfully requested to withdraw the rejection of claims 19-24 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement.

Claims 19-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, Examiner states that the claims are broadly drawn to a method for selectively controlling the transcription of a gene of interest comprising the transformation of a plant with a genetic construct wherein the construct may comprise a multitude of nucleic acid sequences which comprise a ROS operator, and a second transformation of a genetic construct comprising a multitude of ROS repressors. The Examiner alleges that the specification only provides guidance for the full length sequence of SEQ ID NO: 2 as a functioning ROS repressor.

Applicant respectfully disagrees.

The Examiner states "the courts held that to adequately describe a claimed genus, Patent Owner[s] must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus".

As discussed above, the specification clearly exemplifies the utility of both wild type and synthetic ROS to reduce the expression of a gene of interest in a plant. Furthermore, the specification discloses a number of different ROS repressors. Therefore, Applicant respectfully submits that a representative number of the species of repressors have been described and that one of skill in the art would be able to "visualize or recognize the identity of the members of the genus of repressors".

In view of the above comments, Examiner is respectfully requested to withdraw the rejection of claims 19-24 under 35 U.S.C. 112, first paragraph for failing to comply with the written description requirement.

CLAIM REJECTIONS - 35 USC § 103

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ulmasov et al. (1997 The Plant Cell 9:1963-1971). The Examiner alleges that Ulmasov et al. teach a plant cotransfected with two constructs, the first construct comprising a reporter gene and DR5 Aux Res, the second construct comprising soybean Aux22 wherein the expression of the reporter gene was repressed by the operator binding and repressor activity of Aux22.

Applicant respectfully traverses the rejection.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. 103(a), there must be (1) some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)); and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. 103, in order to set forth a case of *prima facie* obviousness the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). MPEP 2143 states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference . . . must teach or suggest all the claim limitations.

In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

THE CLAIMS

Claim 24 is directed to a method for selectively controlling the transcription of a gene of interest by crossing a first plant with a second plant. The first plant comprises a first genetic construct comprising a first regulatory region operatively linked to a gene of interest and a repressor operator sequence capable of controlling the activity of the first regulatory region. The second plant comprises a second genetic construct comprising a second regulatory region in operative association with a nucleic acid molecule encoding a repressor. The repressor exhibits both repressor operator binding activity and repressor activity. Furthermore, the repressor is optimized for plant expression. The progeny obtained by the cross comprises both the first and second genetic construct and expression of the second genetic construct represses expression of the first genetic construct.

ANALYSIS

Applicant respectfully submits that Ulmasov et al. teaches away from the present invention as the repressor (Aux/IAA proteins, such as Aux22) disclosed in Ulmasov et al. works in a different way than the repressor of the present invention.

In Ulmasov et al. a cotransfection assay with Aux/IAA effector plasmids and AuxRE promoter-GUS reporter genes is disclosed at page 1967. An effector plasmid encoding the soybean Aux/IAA protein Aux 22 was cotransfected into carrot cells with a construct comprising a reporter gene and DR5 AuxREs promoter. Although expression of Aux22 from the effector plasmid resulted in repression of expression of the reporter gene, it is disclosed that repression by Aux/IAA proteins results from direct interaction between Aux/IAA proteins (such as Aux22) and auxin response transcription factors (ARFs) and that this interaction either prevents ARFs from binding to auxin response element (AuxRE) or prevent ARFs, when bound to AuxREs, from interacting with cofactors that are required for AuxRE activity (page 1969, 2nd column, last paragraph).

The repressor of the present invention exhibits both repressor operator binding activity and repressor activity. In contrast, gel mobility shift assays shown in Figure 4 of Ulmasov et al. (page 1966) demonstrate that ARF1 binds to DR5 AuxRE, and that Aux/IAA proteins including soybean Aux22 failed to bind the DR5 AuxRE probe. Yeast two hybrid data (page 1966-1967) shows that Aux/IAA protein interact with ARF1. Ulmasov et al. state that "these results indicate that ARF1 and other ARF proteins are DNA binding proteins that recognize TGTCTC AuxRE target sites but that Aux/IAA proteins do not recognize and bind to these same AuxREs". Ulmasov et al. teach that Aux/IAA proteins act as repressors of AuxRE-GUS reporter gene expression without Aux/IAA proteins binding directly to TGTCTC elements of AuxRE. The Aux/IAA proteins act as repressors only through association with ARF1. The Aux/IAA proteins do not have DNA binding activity.

There is no teaching that the Aux/IAA protein taught by Ulmasov et al. exhibits both repressor operator binding activity and repressor activity as defined in claim 24.

Applicant respectfully submits that the Examiner has not set forth a *prima facie* case of obviousness under 35 U.S.C. 103(a).

Only the present invention teaches the method for selectively controlling the transcription of a gene of interest using a nucleic acid molecule encoding a repressor that exhibits both repressor operator binding activity and repressor activity. Ulmasov et al. does not hint or suggest such a method and in fact teaches away from such a method as discussed above. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983). Applicant respectfully submits that the Examiner has only arrived at the present invention from the disclosure of Ulmasov et al. through the benefit of impermissible hindsight.

The Examiner states Ulmasov et al. did not teach transforming separate plants and mating them to obtain progeny comprising both construct, however, plant transformation methods are well known in the art, and cotransfecting a plant is merely a design choice for transformation. The Examiner alleges that given the state of the art and the disclosure by Ulmasov et al., it would have been therefore obvious for one of ordinary skill in the art to use the constructs designed by Ulmasov et al. and modify the method by transforming each into individual plants and breeding the two plants to obtain progeny comprising both constructs.

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. 103(a), the cited reference(s) must actually teach or suggest the claimed invention (*Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Applicant respectfully submits that even if it were obvious for a person skilled in the art to use the constructs designed by Ulmasov et al. and modify the method by transforming each into individual plants and breeding the two plants to obtain progeny comprising both constructs (which is denied), it is submitted that the skilled person would still not arrive at the claimed invention. In particular, the claimed subject-matter is limited to a method using a nucleic acid molecule which encodes a repressor exhibiting both repressor operator binding activity and repressor activity. Ulmasov et al. does not hint or suggest such a repressor and in fact teaches away from such a repressor as discussed above.

Accordingly, Applicant respectfully submits that the disclosure of Ulmasov et al. does not actually teach or suggest the claimed invention.

Applicant respectfully requests that the rejection of claim 24 under 35 U.S.C. 103(a) be reconsidered and withdrawn.

Claims 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulmasov et al. The Examiner alleges that Ulmasov et al. teach a plant cotransfected with two constructs, the first construct comprising a reporter gene and DR5 Aux Res, the second construct comprising soybean Aux22 wherein the expression of the reporter gene was repressed by the operator binding and repressor activity of Aux22.

THE CLAIMS

Claim 19 is directed to a method for selectively controlling the transcription of a gene of interest by crossing a first plant with a second plant. The first plant comprises a first genetic construct comprising a regulatory region operatively linked to a gene of interest and a ROS operator sequence. The second plant comprises a second genetic construct comprising a regulatory region in operative association with a nucleic acid molecule encoding a ROS repressor. The ROS repressor exhibits both ROS operator binding activity and ROS repressor activity. The progeny obtained by the cross comprises both the first and second genetic construct and expression of the second genetic construct represses expression of the first genetic construct. Claim 20 is dependent on claim 19.

Claims 21, 22 and 23 are similar to claim 19, however the first and second genetic construct are introduced into a single plant instead of crossing two plants.

ANALYSIS

There is no hint or suggestion in Ulmasov et al. of a method for selectively controlling the transcription of a gene of interest using a ROS operator sequence and a nucleic acid molecule encoding a ROS repressor exhibiting both ROS operator binding activity and ROS

repressor activity. Instead Ulmasov et al. discloses that overexpression of Aux/IAA proteins in carrot cells causes repression of TGTCTC AuxRE activity.

Examiner alleges that the properties of the nucleic acid molecule given in the specification include stringency conditions that are low and interpreted to read on any similar DNA sequence exhibiting ROS repressor activity. Applicant respectfully submits that the Examiner has not set forth a *prima facie* case of obviousness under 35 U.S.C. 103(a).

It is disclosed in paragraph 65 of the specification as filed:

"By "ROS repressor" it is meant any ROS repressor as known within the art. These include the ROS repressor as described herein, as well as other microbial ROS repressors, for example but not limited to ROSAR (Agrobacterium radiobacter, Brightwell et al. (1995) Mol. Plant Microbe Interact. 8: 747-754), MucR (Rhizobium meliloti; Keller M et al., (1995) Mol. Plant Microbe Interact. 8: 267-277), and ROSR (Rhizobium elti; Bittinger et al., (1997) Mol. Plant Microbe Interact. 10: 180-186; also see Cooley et al. 1991, J. Bacteriol. 173: 2608-2616; Chou et al., 1998, Proc. Natl. Acad. Sci., 95: 5293; Archdeacon J et al. 2000, FEMS Microbiol Let. 187: 175-178; D'Souza-Ault M. R., 1993, J Bacteriol 175: 3486-3490; all of which are incorporated herein by reference). Examples of a ROS repressor, which are not to be considered limiting, are provide in FIGS. 1(A) to (C) and (SEQ ID NO's: 1-3 and 21)"

Applicant respectfully submits that Ulmasov et al. teaches away from the present invention as the repressor (Aux/IAA proteins, such as Aux22) disclosed in Ulmasov et al. is not a ROS repressor and in fact works in a different way than the ROS repressor of the present invention.

In Ulmasov et al. a cotransfection assay with Aux/IAA effector plasmids and AuxRE promoter-GUS reporter genes is disclosed at page 1967. An effector plasmid encoding the soybean Aux/IAA protein Aux 22 was cotransfected into carrot cells with construct comprising a reporter gene and DR5 AuxREs promoter. Although expression of Aux22 from

the effector plasmid resulted in repression of expression of the reporter gene, it is disclosed that repression by Aux/IAA proteins results from direct interaction between Aux/IAA proteins (such as Aux22) and auxin response transcription factors (ARFs) and that this interaction either prevents ARFs from binding to auxin response element (AuxRE) or prevent ARFs, when bound to AuxREs, from interacting with cofactors that are required for AuxRE activity (page 1969, 2nd column, last paragraph).

The ROS repressor of the present invention exhibits both ROS repressor operator binding activity and ROS repressor activity. In contrast, it is disclosed in Ulmasov et al. that Aux/IAA proteins act as repressors of AuxRE-GUS reporter gene expression without Aux/IAA proteins binding directly to TGTCTC elements of AuxRE. This is supported by the gel mobility shift assay with ARF1 and Aux/IAA proteins disclosed at page 1966 of Ulmasov et al. The Gel mobility shift assays shown in Figure 4 demonstrate that ARF1 binds to DR5 AuxRE in vitro. Figure 4 also shows that Aux/IAA proteins including soybean Aux22 failed to bind the DR5 AuxRE probe. It is disclosed that "these results indicate that ARF1 and other ARF proteins are DNA binding proteins that recognize TGTCTC AuxRE target sites but that Aux/IAA proteins do not recognize and bind to these same AuxREs". It is also disclosed that ARF1 interacted with Aux/IAA proteins in a yeast two-hybrid system (page 1966-1967).

Applicant respectfully submits that Ulmasov et al. further teaches away from the present invention as the operator sequence (AuxREs) disclosed in Ulmasov et al. is not a ROS operator sequence and in fact works in a different way than the ROS operator sequence of the present invention. It is taught in Ulmasov et al. that with AuxREs, the TGTCTC element causes repression of GUS reporter gene expression in the absence of auxin and activation of expression in the presence of auxin (page 1963, first paragraph). In contrast GUS expression in transgenic plant lines transformed with CaMv 35S promoter-GUS reporter genes modified to contain ROS operator sites, showed high levels of GUS expression without requiring the presence of auxin (see Figure 8). As disclosed at paragraph 72, the ROS operator of the present invention:

"may comprise 9 or more nucleotide base pairs (see FIGS. 1(D) and (E)) that exhibits the property of binding a DNA binding domain of a ROS repressor. A

consensus sequence of a 10 base pair region including the 9 base pair DNA binding site sequence is WATDHWKMAR (SEQ ID NO: 20; FIG. 1(E)). The last nucleotide, "R", of the consensus sequence is not required for ROS binding (data not presented). Examples of operator sequences, which are not to be considered limiting in any manner, also include, as is the case with the ROS operator sequence from the virC or virD gene promoters, a ROS operator made up of two 11 bp inverted repeats separated by TTTA:

TATATTTCAATTTTATTGTAATATA; (SEQ ID NO: 8) or

the operator sequence of the IPT gene:

TATAATTAAAATATTAAGTCTGCATT. (SEQ ID NO: 19)."

There is no hint or suggestion of such a ROS operator sequence in Ulmasov et al.

Applicant respectfully submits that the Examiner has not set forth a *prima facie* case of obviousness under 35 U.S.C. 103(a).

Only the present invention teaches the method for selectively controlling the transcription of a gene of interest using a ROS operator sequence and a nucleic acid molecule encoding a ROS repressor exhibiting both ROS operator binding activity and ROS repressor activity. Ulmasov et al. does not hint or suggest such a method and in fact teaches away from such as method as discussed above. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983). Applicant respectfully submits that the Examiner has only arrived at the present invention from the disclosure of Ulmasov et al. through the benefit of impermissible hindsight.

The Examiner states Ulmasov et al. did not teach breeding steps, nuclear localization signals, or inducible or tissue specific promoters. However, plant transformation methods including breeding steps, nuclear localization signals and inducible and tissue specific promoters are well known in the art and represent design choices that would be obvious to one of ordinary skill in the art to apply to a plant system. The Examiner alleges that given the state of the art and the disclosure by Ulmasov et al., it would have been therefore obvious for one of ordinary skill in the art to use the constructs designed by Ulmasov et al. and modify the method by transforming each into individual plants and breeding the two plants to obtain progeny comprising both constructs, and add nuclear localization signal sequences and inducible or tissue specific promoters.

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. 103(a), the cited reference(s) must actually teach or suggest the claimed invention (*Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980)). Applicant respectfully submits that even if it were obvious for a person skilled in the art to use the constructs designed by Ulmasov et al. and modify the method by transforming each into individual plants and breeding the two plants to obtain progeny comprising both constructs (which is denied), it is submitted that the skilled person would still not arrive at the claimed invention. In particular, the claimed subject-matter is limited to a method using a ROS operator sequence and a nucleic acid molecule encoding a ROS repressor exhibiting both ROS operator binding activity and ROS repressor activity. Ulmasov et al. does not hint or suggest such a ROS operator or ROS repressor and in fact teaches away from such an operator and repressor as discussed above.

Accordingly, Applicant respectfully submits that the disclosure of Ulmasov et al. does not actually teach or suggest the claimed invention.

Applicant respectfully requests that the rejection of claim 19-23 under 35 U.S.C. 103(a) be reconsidered and withdrawn.

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Amendment & Response

It is respectfully submitted that the above-identified application is now in condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, she is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,



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